HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index

Nöroendokrin Tümörlerde Evreleme Galyum-68 Dotatate PET/BT Görüntüleme: Primer Tümör SUVmax Değeri ile Patolojik Grade ve Ki-67 Proliferasyon İndeksi Arasındaki İlişki

Özge Vural Topuz[1,*] | Emin Büyüktalancı[2]

[1]University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Department of Nuclear Medicine, Istanbul, Türkiye
[2]University of Health Sciences, Başakşehir Çam and Sakura City Hospital, Department of Pathology, Istanbul, Türkiye

Sorumlu Yazar | Correspondence Author
Özge Vural Topuz
ozgevuraltopuz@gmail.com
Address for Correspondence: University of Health Sciences Başakşehir Çam and Sakura City Hospital, Department of Nuclear medicine Başakşehir, İstanbul, 34000, Türkiye

Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1605027
Geliş Tarihi | Received: 21.12.2024
Kabul Tarihi | Accepted: 30.01.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Vural Topuz Ö, Büyüktalancı E. Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index. Hitit Medical Journal 2025;7(1):101-108. https://doi.org/10.52827/hititmedj.1605027

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu çalışma Başakşehir Çam ve Sakura Şehir Hastanesi Etik Kurulu tarafından onaylandı (Tarih: Temmuz 2024; Onay numarası: E-96317027-514.10-248465455).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez:ÖVT,EB Tasarım: ÖVT,EB Veri Toplama/Veri İşleme: ÖVT,EB Veri Analizi: ÖVT,EB Makalenin Hazırlanması: ÖVT,EB
Hasta Onamı: Gerek yok.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This study was approved by the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (Date: July 2024; Approval number: E-96317027-514.10-248465455).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ÖVT,EB Design: ÖVT,EB Data Collection/Data Processing: ÖVT,EB Data Analysis: ÖVT,EB Manuscript Preparation: ÖVT,EB
Informed Consent: Not applicable
Financial Disclosure: There are no financial funds for this article.
Copyright & License: Authors publishing with the journal retain the copyright of their work licensed under CC BY-NC 4.0.

Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index

ABSTRACT

Objective: To determine whether the maximum standardized uptake value SUVmax of the primary lesion measured via Ga-68 DOTATATE PET/CT imaging can be used to predict histological grade and Ki-67 proliferation index in treatment-naïve neuroendocrine tumors (NETs).

Material and Method: A total of 57 patients diagnosed with NET who underwent Ga-68 DOTATATE PET/CT between January 2021 and April 2024 were retrospectively evaluated. Patient data including age, histopathology, primary tumor localization, tumor size, Ki-67 proliferation index, histological grade, and SUVmax values from the same tumor were recorded. Histological grades 2 and 3 were pooled into a single group (grade 2&3).

Results: The mean age was 49.44 ± 17.20 years. The most common biopsy locations were the liver (28.07%), stomach (21.05%), and pancreas (19.30%). Median Ki-67 proliferation index was 5 (interquartile range: 2–8). Grade 1 tumors were present in 19 patients (33.33%), grade 2 tumors in 35 patients (61.40%), and grade 3 tumors in 3 patients (5.26%). The SUVmax values were positively correlated with tumor size and Ki-67 proliferation index, and Ki-67 proliferation index was positively correlated with tumor size and mitotic count. Patients with grade 2&3 tumors had significantly higher SUVmax values and were older compared to those with grade 1 tumors. For predicting grade 2&3 tumors, the SUVmax value had an area under the ROC curve value of 0.669 (95% CI: 0.526–0.811, *p=0.039*), which yielded an overall accuracy of 64.91%, with 57.89% sensitivity, 78.95% specificity, 84.62% positive predictive value, and 48.39% negative predictive value, at a cut-off value of >12.5.

Conclusion: Initial Ga-68 DOTATATE PET/CT imaging in NETs demonstrated that the SUVmax value of the primary lesion is positively correlated with Ki-67 proliferation index. A maximum standardized uptake value threshold of >12.5 g/ml was shown to distinguish grade 2&3 tumors at an early stage with high positive predictive value.

Keywords: DOTATATE, NETs, PET, Ga-68, SUVmax.

ÖZET

Amaç: Nöroendokrin tümörlerde (NET) tedavi öncesi Ga-68 DOTATATE PET/BT görüntülemede primer lezyon maximum standartlaştırılmış alım değerinin SUVmax histolojik derece ve Ki-67 proliferasyon indeksini öngörmedeki rolünü belirlemektir.

Gereç ve Yöntem: Ocak 2021-Nisan 2024 tarihleri arasında Ga-68 DOTATATE PET/BT görüntülemesi yapılmış 57 nöroendokrin tümör tanılı hasta retrospektif değerlendirildi. Hastaların yaş, histopatoloji, primer tümör lokalizasyonları, tümör boyutları, Ki-67 proliferasyon indeksleri, histolojik dereceleri ve tümör SUVmax değerleri kayıt edildi. Histolojik derece 2 ve 3 grup bir arada gruplandı (derece 2&3).

Bulgular: Yaş ortalaması 49,44 ± 17,20 idi. En sık biyopsi lokasyonları karaciğer (%28,07), mide (%21,05) ve pankreas (%19,30) idi. Ortalama Ki-67 proliferasyon indeksi 5 idi (çeyrekler açıklığı: 2 - 8). 19 hastada (% 33,33) derece 1, 35 hastada derece 2 (% 61,40) ve 3 hastada derece 3 tümör (%5,26) vardı. Tümörlerin SUVmax değerleri, tümör boyutları ve Ki-67 proliferasyon indeksleri ile, Ki-67 proliferasyon indeksleri de tümör boyutları ve mitoz sayıları ile pozitif korele idi. Derece 2&3 tümörlü hastalar daha ileri yaşlı olup tümör SUVmax değerleri derece 1 tümörlere göre anlamlı olarak daha yüksekti. ROC analizinde SUVmax değeri >12,5 eşiğinin derece 2&3 hasta grubunu %57,89 duyarlılık, %78,95 özgüllük, % 64,91doğruluk, % 84,62 pozitif öngörü değeri ve % 48,39 negatif öngörü değeri ile ayırt edebildiği gösterildi (EAA: 0,669, 95% CI: 0,526-0,811, *p=0,039*).

Sonuç: Nöroendokrin tümörlerde inisyal Ga-68 DOTATATE PET/BT'de primer tümöre ait SUVmax değerinin Ki-67 proliferasyon indeksleri ile pozitif korele olduğu ve 12,5 g/ml eşik değerinin üzerinde olmasının derece 2&3 hastaları erken dönemde yüksek pozitif öngörü değeri ile ayırt edebildiği gösterildi.

Anahtar Sözcükler: DOTATATE, Ga-68, NET, SUVmax, PET.

Introduction

Neuroendocrine tumors (NETs) are rare malignant neoplasms originating from neuroendocrine cells in various organs, which often express somatostatin receptors (SSTRs) on their surfaces (1). Their primary origin is the gastrointestinal tract (two-thirds) and pancreas, with 25% emerging from the bronchopulmonary tract, and rarely from other locations (2).

NETs are diagnosed pathologically and are classified into histological grades based on mitotic counts and Ki-67 proliferation index (PI). According to the 5th edition of the World Health Organization classification and grading criteria for digestive and thoracic NETs, patients are classified as low grade (grade 1), intermediate grade (grade 2), and high grade (grade 3) (3). For digestive NETs, patients with <2 mitoses/2 mm^2 or a Ki-67 PI of <3% are classified as grade 1, those with 2–20 mitoses/2 mm^2 or Ki-67 PI 3–20% as grade 2, and those with >20 mitoses/2 mm^2 or Ki-67 PI >20% as grade 3 (3). For thoracic NETs, patients with <2 mitoses/2 mm^2 are classified as grade 1; those with 2–10 mitoses/2 mm^2 as grade 2; and those with >10 mitoses/2 mm^2 and/or Ki-67 PI >30% as grade 3 (4,5).

It is well-established that NETs exhibit varying degrees of invasive biological behavior based on histological grade, which makes accurate grading and Ki-67 PI measurement critical for prognostication and management (6). These features are typically determined through post-surgical histopathological examination or invasive biopsy, and therefore, non-invasive methods that can aid in the early prediction of these characteristics can be highly beneficial.
Approximately 90% of NETs overexpress SSTRs on the cell membrane, making these receptors a key target for NET imaging and therapy (7). Positron emission tomography / computed tomography (PET/CT) with Gallium-68 (Ga-68)-labeled somatostatin analogs enables visualization of NETs by binding to SSTR subtypes 2 and 5 (8). Approved for use by the Food and Drug Administration in 2016, Ga-68 DOTATATE specifically binds to overexpressed SSTRs and is widely used in the initial staging of NETs, localization of primary tumors, preoperative staging, and patient selection for peptide receptor radionuclide therapy (9).

The most commonly used semi-quantitative parameter in PET imaging is the maximum standardized uptake value (SUVmax), which provides a numerical value allowing the assessment of tumoral radiopharmaceutical retention and tumor-to-background activity ratio, alongside qualitative visual data (10).

Our aim was to investigate whether the primary-lesion SUVmax value obtained from Ga-68 DOTATATE PET/CT could predict the histological grade and/or the Ki-67 PI of treatment naive NETs.

Material and Method

Patient Selection and Preparation

Patients who underwent Ga-68 DOTATATE PET/CT imaging in our nuclear medicine unit between January 2021 and April 2024 with a diagnosis of NET were retrospectively evaluated. Inclusion criteria were having a histopathological diagnosis of NET, a time interval of less than 1 month between biopsy and Ga-68 DOTATATE PET/CT imaging, not having received prior treatment or surgery, and absence of additional malignancy diagnoses. Patients were excluded if they lacked a definitive histopathological diagnosis, had a biopsy-to-imaging interval greater than 1 month, had undergone surgery or received treatment, or had concurrent malignancies.
This study was approved by the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (Date: July 2024; Approval number: E-96317027-514.10-248465455). All diagnostic and therapeutic procedures were conducted in compliance with local national guidelines and the principles of the Declaration of Helsinki (1964) and its later amendments.

Ga-68 DOTATATE PET/CT imaging Image Acquisition

Prior to PET/CT imaging, patients were informed about the procedure both orally and in written form. The Ga-68 DOTATATE injection was performed (120-200 MBq) (80µg peptide per 14 mci), followed by a resting period of around 45-60 minutes. The patients were directed to assume a supine position for the imaging process and acquisition was performed from the vertex to the mid-thigh (Philips Ingenuity TF 64 PET/CT; Philips Medical Systems, OH, USA). Non-contrast CT obtained with low dosage exposure was used for attenuation correction, with 4-mm slice thickness and employing 113 mAS and 120 kV

settings. After completion of the CT, a 4-minutes-per-bed PET image acquisition was carried out. Reconstruction of images was performed with an iterative method that generated cross-sectional images on coronal and sagittal planes, as well as 3-dimensional projections.

Image Analysis

Ga-68 DOTATATE PET/CT images were analyzed by two experienced nuclear medicine specialists. In cases of disagreement, a consensus was reached through detailed discussion. SUVmax values were recorded by drawing a volume of interest around the primary lesion.

Table I. Summary of variables

Age	49.44 ± 17.20
Sex	
Male	25 (43.86%)
Female	32 (56.14%)
Location	
Lung	5 (8.77%)
Gastric	12 (21.05%)
Pancreas	11 (19.30%)
Liver	16 (28.07%)
Small bowel	4 (7.02%)
Colon	5 (8.77%)
Rectum	4 (7.02%)
SUVmax	10.5 (4.9 - 31.0)
Tumor size (cm)	3.0 (1.7 - 5.9)
Ki-67 (%)	5 (2 - 8)
Grade	
Grade 1	19 (33.33%)
Grade 2	35 (61.40%)
Grade 3	3 (5.26%)
Mitosis	1 (0 - 3)
Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.	

Pathology

Histopathological diagnoses, Ki-67 PI, and mitotic counts were assessed using pathology slides. For Ki-67 PI, immunohistochemical staining was applied to the slides and 500–2000 neoplastic cells were evaluated at 400X magnification. Cells showing nuclear staining in the hotspot areas (regions with the most intense staining) were considered regardless of staining intensity. The percentage ratio of tumor cells stained with Ki-67 to the total tumor cells in the selected area was defined as Ki-67 PI (11).

Table II. Correlations between variables

		Tumor size (cm)	Ki-67 (%)	Mitosis
SUVmax	*r*	*0.326*	*0.368*	*0.107*
	p	***0.013***	***0.005***	*0.426*
Tumor size (cm)	r		*0.407*	*0.126*
	p		***0.002***	*0.348*
Ki-67 (%)	r			*0.488*
	p			***<0.001***
r: Spearman correlation coefficient				

Mitotic counts were assessed on H&E (Hematoxylin-Eosin) stained slides and slides stained immunohistochemically with PHH3. Counts were performed over at least 10 mm^2, and the number of mitoses per 2 mm^2 was recorded as standard in tumor regions with the highest mitotic activity (corresponding to 10 high-power fields at 400X magnification).

Table III. Summary of variables with regard to grade

	Grade			
	Grade 1 (n=19)	Grade 2&3 (n=38)	Test statistic	*p*
Age	41.79 ± 18.10	53.26 ± 15.60	Student's t test, t=-2.481	***0.016***
Sex				
Male	9 (47.37%)	16 (42.11%)	Chi-square test, X^2=0.009	*0.925*
Female	10 (52.63%)	22 (57.89%)		
Location				
Lung	1 (5.26%)	4 (10.53%)	Fisher-Freeman-Halton test, Exact=2.566	*0.908*
Gastric	6 (31.58%)	6 (15.79%)		
Pancreas	3 (15.79%)	8 (21.05%)		
Liver	5 (26.32%)	11 (28.95%)		
Small bowel	1 (5.26%)	3 (7.89%)		
Colon	2 (10.53%)	3 (7.89%)		
Rectum	1 (5.26%)	3 (7.89%)		
SUVmax	6.1 (4.2 - 12.3)	16.55 (5.9 - 38.2)	MWU test, U=239.0	***0.039***
Tumor size (cm)	2.5 (1.0 - 5.0)	3.75 (1.7 - 6.0)	MWU test, U=288.0	0.216
Ki-67 (%)	1.5 (1 - 2)	7 (5 - 10)	MWU test, U=000.0	***<0.001***
Mitosis	1 (0 - 1)	1 (1 - 5)	MWU test, U=200.5	***0.005***
Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. MWU: Mann Whitney U. Statistically significant p values are shown in bold.				

Table IV. Performance of SUVmax to predict grade 2&3 tumors, ROC curve analysis

Cut-off	>12.5
Sensitivity	57.89%
Specificity	78.95%
Accuracy	64.91%
PPV	84.62%
NPV	48.39%
AUC (95% CI)	0.669 (0.526 - 0.811)
p	0.039

ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence interval

In cases of discordance between mitotic count and Ki-67 PI, the higher value was preferred (12). Grade 2 and grade 3 tumors were combined into a single group designated as the 'grade 2&3' group due to the presence of only three patients with grade 3 tumor –since it would have been inappropriate to perform statistical analysis for a group with only three samples.

Table V. Association between variables and grade 2&3 tumors, multivariable logistic regression analysis

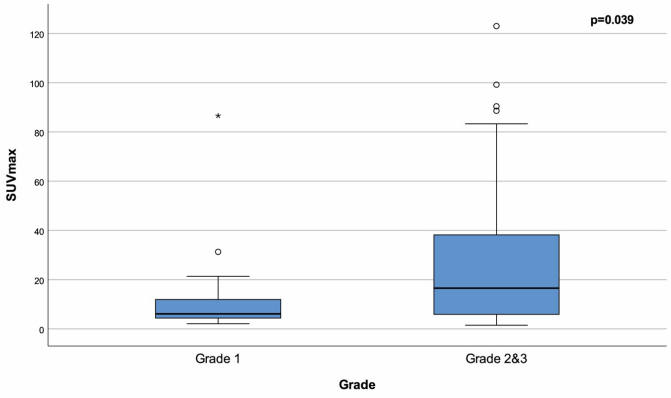
	β coefficient	Standard error	*p*	Exp(β)	95% CI for Exp(β)	
Age	0.055	0.023	***0.017***	1.056	1.010	1.104
SUVmax, >12.5	1.895	0.769	***0.014***	6.654	1.473	30.051
Mitosis	0.388	0.191	***0.042***	1.474	1.014	2.143
Constant	-3.340	1.290	*0.010*	0.035		

Nagelkerke R^2=0.433, CI: Confidence interval, Statistically significant p values are shown in bold.

Statistical Analysis

A p-value of less than 0.05 was deemed indicative of statistical significance, and all tests were two-tailed. Data analyses were conducted using SPSS version 25.0 (IBM, Armonk, NY, USA). Continuous variables were assessed for normality using histograms and Q-Q plots. Descriptive data were expressed as mean ± standard deviation for normally distributed variables, median (interquartile range) for those not normally distributed, and frequency (percentage) for categorical data. The Student's t-test was used to compare age, which was a normally distributed continuous variable. The Mann-Whitney U test was used for the comparisons of SUVmax, tumor size, Ki-67 and mitosis, which were non-normally distributed continuous variables. Sex (categorical variable) was analyzed with the chi-square test and location (categorical variable) was analyzed with the Fisher-Freeman-Halton test due to the fact that some cells in the confusion matrix had expected counts less than five. Correlations between continuous variables (SUVmax, tumor size, Ki-67 and mitosis) were examined using Spearman's correlation coefficient due to non-normal distribution. Significant factors associated with grade 2&3 tumors were identified through multivariable logistic regression analysis. The initial model included variables found to be statistically significant in univariable analyses.

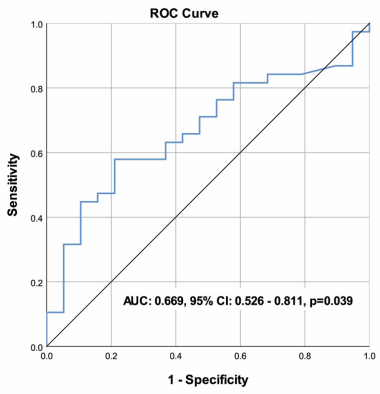
Figure I. Box-plot of the SUVmax with regard to grade



Results

We included 57 patients with NET (25 males and 32 females) into the study, mean age was 49.44 ± 17.20. The most common biopsy locations were the liver (28.07%), stomach (gastric; 21.05%) and pancreas (19.30%). Nineteen (33.33%) patients were grade 1, thirty-five (61.40%) patients were grade 2, and three (5.26%) patients were grade 3. Median Ki-67 PI was 5 (interquartile range 2 - 8) (Table I).

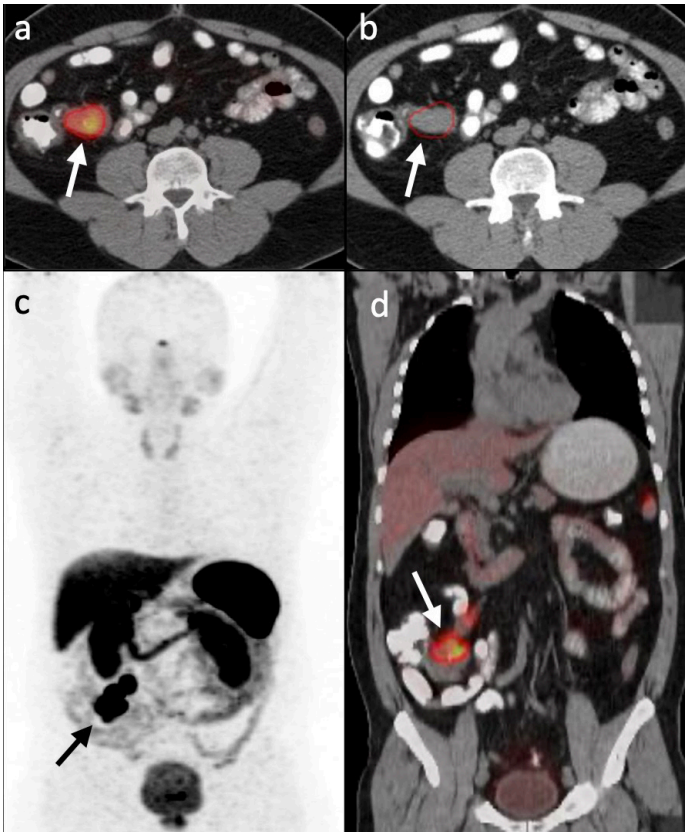
Figure II. ROC curve of the SUVmax value in the prediction of grade 2&3 tumors



Relationship Between SUVmax and Ki-67

SUVmax was positively correlated with tumor size (Spearman correlation coefficient, *r=0.326, p=0.013*) and Ki-67 (Spearman correlation coefficient, *r=0.368, p=0.005*). Ki-67 was positively correlated with the tumor size (Spearman correlation coefficient, *r=0.407, p=0.002*) and it was also correlated with mitosis as anticipated (Spearman correlation coefficient, *r=0.488, p<0.001*). There were no significant relationships between SUVmax and mitosis, and between tumor size and mitosis (Table II).

Figure III. Baseline 68Ga-DOTATATE PET/CT images of a patient with grade 2&3 neuroendocrine tumor in the small intestine with a maximum standard uptake (SUVmax) value of 31.5 g/ml (greater than the >12.5 g/ml threshold). Primary tumor (arrow) on axial fused image (a), axial CT images (b), maximum intensity projection (MIP) image (c) and coronal fused image (d).



Relationship Between SUVmax and Grade

Age (Student's t test, *t=-2.481, p=0.016*), SUVmax (Mann Whitney U test, *U=239.0, p=0.039*) and mitosis (Mann Whitney U test, *U=200.5, p=0.005*) values were significantly higher in grade 2&3 tumors than in grade 1 tumors (Figure I). We found no significant differences between grade 1 and grade 2&3 tumors in terms of sex, location, and tumor size (Table III).

SUVmax had significance in discriminating between grade 1 and grade 2&3 tumors with an area under ROC curve of 0.669 (95% CI: 0.526 - 0.811, *p=0.039*) (Figure II). With an optimal cut-off value of 12.5 (higher values predict grade 2&3 tumors), SUVmax had an overall accuracy of 64.91%, with 57.89% sensitivity, 78.95% specificity, 84.62% positive predictive value, and 48.39% negative predictive value (Table IV). Logistic regression with a multivariable model adjusted by age (*p=0.017*) showed that grade 2&3 tumors were independently associated with having a high SUVmax (>12.5) (OR: 6.654, 95% CI: 1.473 - 30.051, *p=0.014*) and high mitosis value (OR: 1.474, 95% CI: 1.014 - 2.143, *p=0.042*) (Table V). A representative imaging result is provided in Figure III.

Discussion

In NETs, early and accurate determination of prognostic features such as histological grade and Ki-67 PI is crucial for surgical planning, which is one of the most important treatment steps, as well as other management decisions, the application of correct treatments, and to predict prognosis (13,14). In this study, we concluded that there is a positive correlation between primary lesion SUVmax value and tumor size, and Ki-67 PI in early staging Ga-68 DOTATATE PET/CT imaging in NETs. In fact, SUVmax values of >12.5 appear to predict grade 2&3 tumors with a high positive predictive value (84.62%). Although the sensitivity and specificity are not very high, we think that these findings may have clinical relevance for the purpose of distinguishing grade 2&3 NETs with non-invasive imaging in the preoperative period – particularly considering the paucity of evidence on this subject.

Prior studies evaluating the relationship between the SUVmax value (obtained from Ga-68 labeled somatostatin analogues PET/CT) and histopathological findings in NETs evaluate the results based on pathological findings of the lesion with the highest SUVmax value and any biopsied lesion. Unlike our study, this approach carries the risk of ignoring the heterogeneous distribution of the disease (15,16). It has been shown that the lesion with the highest SUVmax value may be pathologically dissimilar to the biopsied lesion. Furthermore, the heterogeneity

of primary and metastatic lesions may be different, and it is also possible that even metastatic lesions located in the same organ (liver) in the same patient may have different histologic grades (17). Chan et al., in their study of lesion SUVmax values obtained from Ga-68 DOTATOC imaging and the pathology results of the same NET lesions, reported an inverse correlation between Ki-67 PI and SUVmax. They stated that this may be due to the lack of correlation between tumor size and SSTRs uptake in their patient population (18). Although the methodology was similar to ours, we report positive correlations between lesion SUVmax, tumor size and Ki-67 PI values, and we believe that the difference may be attributed to patient characteristics and the types of compounds used during imaging. Nonetheless, these results necessitate the investigation of how the SUVmax-tumor size relationship might be associated with the correlations between SUVmax and Ki-67.

Although NETs generally show high SSTRs expression similar to the neuroendocrine cells from which they originate (since they are well-differentiated tumors), it is also known that SSTR expression declines in poorly differentiated tumors (19). Similarly, a decrease in Ga-68 DOTATATE uptake and lower SUVmax values are expected in poorly-differentiated neuroendocrine carcinomas with Ki-67 PI values of >55% due to loss of SSTR expression (9). In a study in which the majority of the patient population (84.6%) consisted of patients with strongly-positive Ki-67 PI values, a negative correlation was reported between Ki-67 PI and Ga-68 DOTATATE SUVmax values (20). There are other studies in the literature reporting that SUVmax value is lower in higher grade patients with high Ki-67 PI compared to those with low grade tumors (16,21). The reason for the positive correlation between Ki-67 PI and SUVmax in our patient population might be associated with the generally low Ki-67 PI values detected in the cohort –with a 75% percentile value of 8%. This again demonstrates the heterogeneity of the disease and warrants further studies with larger patient groups.

Tumor histological grade can traditionally be determined by percutaneous core biopsies or surgical excision from the most easily and safely accessible region of the lesion (19). There may be differences in histopathological findings depending on the site of biopsy, which can be explained by tumor heterogeneity, and therefore it is possible to obtain different histologic grades from biopsy material acquired from different regions of the lesion (19). In our study, a SUVmax value of >12.5 g/ml obtained from the tumor was found to be relatively capable in predicting grade 2&3 lesions with a high positive predictive value. This supports the literature on this topic by revealing that molecular imaging with Ga-68 DOTATATE PET/CT can benefit the characterization of lesions that are observed throughout the body (22,23). Being able to differentiate grade 2&3 and grade 1 lesions non-invasively in the early period may facilitate better planning of personalized treatments (13), which could improve outcomes.

The limitations of the study are that it was single centered, retrospective in design, consisted of a small number of patients, and there were considerably fewer grade 3 patients compared to other groups (5.26%). Another limitation is that other volumetric parameters that can be obtained from these lesions (such as MTV and TLG) were not examined in the Ga-68 DOTATATE PET/CT imaging of individuals.

Conclusion

Our study demonstrated that a SUVmax threshold value of >12.5 g/ml obtained non-invasively from the initial Ga-68 DOTATATE PET/CT study of the primary lesion in patients with NETs can distinguish grade 2&3 patients from grade 1 patients with a high positive predictive value and a respectable specificity. We also found that SUVmax value was positively correlated with Ki-67 PI, another important prognostic marker of the disease.

References

1. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61-72.
2. Tirosh A, Papadakis GZ, Millo C, et al. Prognostic Utility of Total 68Ga-DOTATATE-Avid Tumor Volume in Patients with Neuroendocrine Tumors. Gastroenterology 2018;154:998-1008.
3. Nagtegaal ID, Odze RD, Klimstra D, et al. WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76:182-188.
4. Travis WD. Pathology and diagnosis of neuroendocrine tumors: lung neuroendocrine. Thorac Surg Clin 2014;24:257-266.

5. Vocino Trucco G, Righi L, Volante M, Papotti M. Updates on lung neuroendocrine neoplasm classification. Histopathology 2024;84:67-85.
6. Ma J, Wang X, Tang M, Zhang C. Preoperative prediction of pancreatic neuroendocrine tumor grade based on 68Ga-DOTATATE PET/CT. Endocrine 2024;83:502-510.
7. Piscopo L, Zampella E, Pellegrino S, et al. Diagnosis, management and theragnostic approach of gastro-entero-pancreatic neuroendocrine neoplasms. Cancers (Basel) 2023;15:3483.
8. Ebner R, Sheikh GT, Brendel M, Ricke J, Cyran CC. ESR Essentials: role of PET/CT in neuroendocrine tumors-practice recommendations by the European Society for Hybrid, Molecular and Translational Imaging. Eur Radiol Published online October 10, 2024.
9. Hope TA, Allen-Auerbach M, Bodei L, et al. SNMMI Procedure Standard/EANM Practice Guideline for SSTR PET: Imaging Neuroendocrine Tumors. J Nucl Med 2023;64:204-210.
10. Teker F, Elboga U. Is SUVmax a useful marker for progression-free survival in patients with metastatic GEP-NET receiving 177Lu-DOTATATE therapy? Hell J Nucl Med 2021;24:122-131.
11. Kim JY, Hong SM, Ro JY. Recent updates on grading and classification of neuroendocrine tumors. Ann Diagn Pathol 2017;29:11-16.
12. Klöppel G. Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. Visc Med 2017;33:324–330.
13. Lee L, Ito T, Jensen RT. Prognostic and predictive factors on overall survival and surgical outcomes in pancreatic neuroendocrine tumors: recent advances and controversies. Expert Rev Anticancer Ther 2019;19:1029-1050.
14. Ito T, Hijioka S, Masui T et al. Advances in the diagnosis and treatment of pancreatic neuroendocrine neoplasms in Japan. J.Gastroenterol 2017;52:9-18.
15. Karls S, Gold R, Kravets S, et al. Correlation of 68Ga-DOTATATE uptake on PET/CT with pathologic features of cellular proliferation in neuroendocrine neoplasms. Ann Nucl Med 2021;35:1066-1077.
16. Kaewput C, Suppiah S, Vinjamuri S. Correlation between Standardized Uptake Value of 68Ga-DOTA-NOC Positron Emission Tomography/Computed Tomography and Pathological Classification of Neuroendocrine Tumors. World J Nucl Med 2018;17:34-40.
17. Shi C, Gonzalez RS, Zhao Z, et al. Liver metastases of small intestine neuroendocrine tumors: Ki-67 heterogeneity and World Health Organization grade discordance with primary tumors. Am J Clin Pathol 2015;143:398–404.
18. Chan H, Moseley C, Zhang L, et al. Correlation of DOTATOC Uptake and Pathologic Grade in Neuroendocrine Tumors. Pancreas 2019;48:948-952.
19. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics 2015;35:500-516.
20. Panagiotidis E, Alshammari A, Michopoulou S, et al. Comparison of the Impact of 68Ga-DOTATATE and 18F-FDG PET/CT on Clinical Management in Patients with Neuroendocrine Tumors. J Nucl Med 2017;58:91-96.
21. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3- octreotate) and 18F-FDG. Cancer 2008;112:2447-2455.
22. Hofman MS, Hicks RJ. Changing paradigms with molecular imaging of neuroendocrine tumors. Discov Med 2012;14:71-81.
23. Maman A. Incidental Papillary Thyroid Carcinoma Detected by Ga-68 DOTATATE PET/CT: A Rare Case Study and Clinical Considerations. Nuklearmedizin. 2024;63:270-271.